

# **EXHIBIT**

# **N**

PATENT  
Attorney Docket No. P-257-US7  
Customer No. 27038

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of )  
Grahame Woollam ) Confirmation No. 9930  
)  
Application No. 16/130,079 ) Group Art Unit 1627  
)  
Filed: September 13, 2018 ) Examiner: Sarah Pihonak  
)  
For: CRYSTALLINE FREEBASE FORMS )  
OF A BIPHENYL COMPOUND )

**RESPONSE PURSUANT TO 37 C.F.R. §1.111**

**Mail Stop Amendment**  
Commissioner for Patents  
P. O. Box 1450  
Alexandria, VA 22313-1450

Sir:

This reply is being filed in response to the Office Action dated May 14, 2019, in the above-identified patent application. The Office Action set a three-month period for response and therefore, this reply is due on or before August 14, 2019. In response to the Office Action, entry of the following amendments and consideration of the following remarks is respectfully requested.

**Amendments to the Claims** begin on page 2 of paper.

**Remarks** begin on page 3 of this paper.

**Electronic Acknowledgement Receipt**

<b>EFS ID:</b>	36529065
<b>Application Number:</b>	16130079
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	9930
<b>Title of Invention:</b>	CRYSTALLINE FREEBASE FORMS OF A BIPHENYL COMPOUND
<b>First Named Inventor/Applicant Name:</b>	Grahame Woollam
<b>Customer Number:</b>	27038
<b>Filer:</b>	Jeffrey Hagenah/Lhet Chuakay
<b>Filer Authorized By:</b>	Jeffrey Hagenah
<b>Attorney Docket Number:</b>	P-257-US7
<b>Receipt Date:</b>	10-JUL-2019
<b>Filing Date:</b>	13-SEP-2018
<b>Time Stamp:</b>	12:17:09
<b>Application Type:</b>	Utility under 35 USC 111(a)

**Payment information:**

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**File Listing:**

Document Number	Document Description	File Name	File Size(Bytes)/Message Digest	Multi Part /.zip	Pages (if appl.)
1		P-257-US7-2019-07-10_Response_to_OA.pdf	139426 aafdc5e79cbaeda90ceb4cf6060735fad1f12 b2c4	yes	10

	Document Description	Start	End
	Applicant Arguments/Remarks Made in an Amendment	3	10
	Claims	2	2
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
<b>Warnings:</b>			
<b>Information:</b>			
<b>Total Files Size (in bytes):</b>		139426	

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**New Applications Under 35 U.S.C. 111**

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

**National Stage of an International Application under 35 U.S.C. 371**

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

**New International Application Filed with the USPTO as a Receiving Office**

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

**REMARKS**

Applicants respectfully request entry of the above amendments and reconsideration of this application in view of the following remarks.

1. **Status of the Claims**

Claims 21-24 are pending in this application. No claims have been added or canceled in this paper and therefore, Claims 21-24 remain pending for examination on the merits.

2. **Summary of the Amendments**

Claims 22 and 24 have been amended to delete the term “substantially.” Entry of these amendments is respectfully requested.

3. **Rejections Under 35 U.S.C. §112, Second Paragraph**

Claims 22 and 24 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. Specifically, the Examiner has indicated that the term “substantially” in Claims 22 and 24 renders these claims indefinite. While not agreeing with this conclusion, in order to expedite prosecution of this application, Applicants have amended Claims 22 and 24 to delete the term “substantially.” Accordingly, the rejection of Claims 22 and 24 under 35 U.S.C. §112, second paragraph, can be withdrawn.

4. **Rejections Under 35 U.S.C. §103**

Claims 21-24 have been rejected under pre-AIA 35 U.S.C. §103(a) as being unpatentable over Axt et al., WO 2006/099165 A1 (“Axt”). Specifically, the Office Action indicates that Axt teaches crystalline forms of the present compound having a melting point above 70 °C, including a crystalline salt form having a melting point of about 150 °C, and that Axt teaches methods of preparing such crystalline forms which are allegedly similar to the methods used to prepare the presently claimed crystalline freebase form having a melting point of about 125 °C. In view of the teachings in Axt, the Office Action concludes:

...it would have been *prima facie* obvious that the crystalline freebase form of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester as described in Axt would have included the crystalline freebase form recited in the present claims, and that the crystalline freebase form as taught by Axt would have had the same characteristics as a result, including a m.p. of about 125 °C and DSC thermogram in accordance with Fig. 4, in the absence of evidence to the contrary. (Office Action at page 5-6)

Applicants respectfully disagree with this conclusion for at least the following reasons.

The pending claims are directed to a crystalline freebase of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester having a melting point of about 125 °C or a differential scanning calorimetry thermogram in accordance with that shown in FIG. 4; and to pharmaceutical compositions comprising the crystalline freebase and a pharmaceutically acceptable carrier. The specification also describes another crystalline freebase having a melting point of about 119 °C but this form is not included in the present claims. These crystalline freebase forms are designated as Form III and IV, respectively.

At the time the present application was filed, Axt described two crystalline freebase forms of the compound which are designated by Axt as Form I and Form II (e.g. Axt at page 10, line 26 to page 11, line 32). Axt also described various crystalline salt forms of the compound including a diphosphate salt having a melting point of about 154.5 °C.<sup>1</sup> Thus, between Axt and the present application, four crystalline freebase forms of the compound are known. These four crystalline freebase forms are summarized in Table A:

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<sup>1</sup> These crystalline salt forms are very different from the crystalline freebase forms in that the crystalline salt forms have a counter ion (such as phosphate) whereas the crystalline freebase forms do not.

**Table A**  
**Crystalline Freebase Forms**

Form	Melting Point <sup>†</sup>	Crystallization Solvent <sup>‡</sup>
Form I	<b>102.7 °C</b> (Axt at page 40, line 11)	<b>Acetonitrile/water mixture</b> (Axt at page 37, line 06)
Form II	<b>98.6 °C</b> (Axt at page 40, line 15)	<b>Acetonitrile/MTBE mixture</b> (Axt at page 38, lines 21-22)
Form III	<b>125 °C</b> (Appl. at page 10, line 25)	<b>Acetonitrile or toluene</b> (Appl. at page 27, line 30 and page 29, line 06)
Form IV	<b>119 °C</b> (Appl. at page 10, line 28)	<b>Acetonitrile</b> (Appl. at page 29, line 20)

<sup>†</sup> Approximate melting point reported by Axt or present application.

<sup>‡</sup> Crystallization solvent reported by Axt or present application.

It is readily apparent from Table A that the crystalline freebase forms disclosed in Axt (Form I and II) have distinct melting points and are prepared from different crystallization solvents compare to the crystalline freebase forms disclosed in the present application (Forms III and IV). The melting points of the crystalline freebase forms disclosed by Axt are both below 103 °C whereas the melting points of the crystalline freebase forms disclosed in the present application are about 119 °C or above – a difference of at least 16 °C. Moreover, the crystalline freebase forms disclosed by Axt are prepared using mixtures of crystallization solvents (acetonitrile/water or acetonitrile/MBTE) whereas the crystalline freebase forms of the present application are prepared using only acetonitrile or toluene, i.e., no co-solvent. Thus, the presently claimed crystalline freebase form, i.e., Form III, is distinct from the crystalline freebase forms disclosed in Axt (i.e., Forms I and II). Form III is prepared under different conditions and it has a significantly higher melting point compared to Forms I and II.<sup>2</sup>

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<sup>2</sup> The Office Action mentions that at least one crystalline salt form disclosed in Axt has a melting point of about 150 °C. However, as previously noted, this crystalline salt form is a diphosphate salt not a crystalline freebase form and

Contrary to the assertions in the Office Action, there is no evidence that the crystalline freebase forms described by Axt include, or are mixtures containing, the crystalline form of the present claims. Axt employs different crystallization solvents than those used in the present application and Axt isolates distinct crystalline freebase forms having significantly different (e.g., lower) melting points compared to the presently claimed crystalline freebase Form III. Moreover, the figures in Axt for crystalline freebase Forms I and II, such as the PXRD patterns (Figures 18 and 23) and DSC traces (Figures 19 and 24), show sharp peaks consistent with pure forms not mixtures. Thus, none of the data reported in Axt suggest that Form I or Form II is actually a mixture containing Form III.

Additionally, nothing in Axt suggests that any other crystalline freebase form of the compound may exist other than Form I and Form II. Nor does Axt suggest how to prepare any other crystalline freebase forms other than Form I and Form II. Axt was clearly trying to prepare as many crystalline forms of the compound as possible and yet Axt did not find the presently claimed crystalline freebase form having a highly desirable, significantly higher melting point. This failure by Axt further supports the conclusion that the presently claimed crystalline freebase form is not obvious in view of Axt.

Thus, in summary, the presently claimed crystalline freebase form is distinct from the crystalline freebase forms disclosed in Axt. The presently claimed crystalline freebase form is prepared under different conditions than those used in Axt and it has different physical properties, i.e., a significantly higher melting point. There is no evidence of record that the procedures described in Axt would have produced the presently claimed crystalline form nor is there any evidence of record that the crystalline freebase forms described in Axt are mixtures that include the presently claimed crystalline freebase form. For at least these reasons, the present rejection of Claims 21-24 under 35 U.S.C. §103(a) as being unpatentable over Axt et al., WO 2006/099165 A1 should be withdrawn.

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therefore, the higher melting point of this crystalline salt form is not relevant when discussing the crystalline freebase forms.

Claims 21-24 have also been rejected under pre-AIA 35 U.S.C. §103(a) as being unpatentable over Mammen et al., U.S. Patent Publication No. 2005/0203133 (“Mammen”). Like Axt, the Office Action argues that Mammen teaches crystalline freebase forms of the compound and methods of preparing such crystalline freebase forms which are allegedly similar to the methods used to prepare the presently claimed crystalline freebase form having a melting point of about 125 °C.

In fact, Mammen teaches the same crystalline freebase forms as Axt, i.e., Forms I and II. This can be seen by comparing the examples in Mammen and Axt. In Example 1D, Mammen prepares a crystalline freebase form from an acetonitrile/water crystallization mixture which is how Axt prepares Form I; and in Example 1E, Mammen prepares a crystalline freebase from an acetonitrile/MTBE crystallization mixture which is how Axt prepares Form II (see, Table A above). The fact that Mammen and Axt produce the same crystalline freebase forms is further illustrated in Table B below which shows a side-by-side comparison of the relevant examples in Axt and Mammen (common text is shown in bold font):

**Table B**  
**Comparison of Examples in Axt and Mammen**

Axt Example 10 (page 37)	Mammen Example 1D (page 21)
<b>230 mg</b> of biphenyl-2-ylcarbamic acid 1-(2- {[4-(4-carbamoylpiperidin-1-ylmethyl) benzoyl] methylamino}ethyl)piperidin-4-yl ester (prepared as described in Example 1) was dissolved in <b>0.2 ml</b> of H <sub>2</sub> O:ACN (1:1), using slight heat. The mixture was then heated in a 70 °C water bath for 2 hours. The heat was turned off and the mixture was allowed to cool to room temperature, then refrigerated at 4 °C for 1 hour. 50 µl of water was then added (oiled out), followed by the addition of 40 µl of ACN to get the sample back into solution. Seeds (crystalline material from Example 8) were added under slow stirring at room temperature. Crystals started to form, and	<b>230 mg</b> of the product of Example 1 was dissolved in <b>0.2 ml</b> of H <sub>2</sub> O:ACN (1:1), using slight heat. The mixture was then heated in a 70°C water bath for 2 hours. The heat was turned off and the mixture was allowed to cool to room temperature, then refrigerated at 4°C for 1 hour. 50 µl of water was then added (oiled out), followed by the addition of 40 µl of ACN to get the sample back into solution. Seeds (synthesis described below) were added under slow stirring at room temperature. Crystals started to form, and the mixture was allowed to sit overnight, with slow stirring. The next day, a heat cool cycle was applied (30°C for 10 minutes, 40°C for 10 minutes,

<p>the mixture was allowed to sit overnight, with slow stirring. The next day, a heat cool cycle was applied (30 °C for 10 minutes, 40 °C for 10 minutes, then 50 °C for 20 minutes). The heat was turned off and the mixture allowed to cool overnight, with slow stirring. The next day, a second heat/cool cycle was applied (60 °C for 1 hour, with dissolving observed at 70 °C). The heat was turned off and the mixture allowed to cool overnight, with slow stirring. The next day, crystals were present and a third heat cool cycle was applied (60 °C for 3 hours). The heat was turned off and the mixture allowed to cool overnight, with slow stirring. The next day, a heat cool cycle was applied (60 °C for 3 hours, slow cool, then 60 °C for 3 hours). The heat was turned off and the mixture allowed to cool overnight, with slow stirring. After 3 days, the solid was filtered and placed on a high vacuum line to remove all solvent and give the title compound.</p>	<p>then 50°C for 20 minutes). The heat was turned off and the mixture allowed to cool overnight, with slow stirring. The next day, a second heat/cool cycle was applied (60°C for 1 hour, with dissolving observed at 70°C). The heat was turned off and the mixture allowed to cool overnight, with slow stirring. The next day, crystals were present and a third heat cool cycle was applied (60°C for 3 hours). The heat was turned off and the mixture allowed to cool overnight, with slow stirring. The next day, a heat cool cycle was applied (60°C for 3 hours, slow cool, then 60°C for 3 hours). The heat was turned off and the mixture allowed to cool overnight, with slow stirring. After 3 days, the solid was filtered and placed on a high vacuum line to remove all solvent and give a freebase crystal of the title compound.</p>
<p style="text-align: center;"><b>Axt</b> <b>Example 11 (page 38)</b></p> <p><b>70 mg</b> of biphenyl-2-ylcarbamic acid 1-(2-{{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester (prepared as described in Example 1) was dissolved in 0.1 mL ACN. After addition of 0.3 ml MTBE, the solution appeared cloudy. An additional 50 µl of ACN was added to clarify the solution (155 mg/ml ACN:MTBE = 1:2). The mixture was left in the vial and capped. Crystals appeared by the next day. The solid was then filtered and placed on a high vacuum line to remove all solvent and give the title compound.</p>	<p style="text-align: center;"><b>Mammen</b> <b>Example 1E (page 22)</b></p> <p><b>70 mg</b> of the product of Example 1 was dissolved in 0.1 mL ACN. After addition of 0.3 ml MTBE, the solution appeared cloudy. An additional 50 µl of ACN was added to clarify the solution (155 mg/ml ACN:MTBE = 1:2). The mixture was left in the vial and capped. A solid appeared by the next day. The solid was then filtered and placed on a high vacuum line to remove all solvent and give a freebase crystal of the title compound.</p>

It is readily apparent from Table B that the procedures disclosed in Axt and Mammen for preparing the crystalline freebase forms of the compound are essentially identical, i.e., they are describing the same experiments. Thus, Axt and Mammen both disclose crystalline freebase Forms I and II. Therefore, like Axt, Mammen does not teach or suggest the presently claimed crystalline freebase form having a melting point of about 125 °C, i.e., Form III.

Accordingly, in summary, the presently claimed crystalline freebase form is distinct from the crystalline freebase forms disclosed in Mammen. The presently claimed crystalline freebase form is prepared under different conditions than those used in Mammen and it has different physical properties, i.e., a significantly higher melting point. There is no evidence of record that the procedures described in Mammen would have produced the presently claimed crystalline form nor is there any evidence of record that the crystalline freebase forms described in Mammen are mixtures that include the presently claimed crystalline freebase form. For at least these reasons, the present rejection of Claims 21-24 under pre-AIA 35 U.S.C. §103(a) as being unpatentable over Mammen et al, U.S. Patent Publication No. 2005/0203133, should be withdrawn.

For the foregoing reasons, Applicants respectfully request that the rejections under pre-AIA 35 U.S.C. §103(a) be withdrawn.

5. Non-Statutory Obviousness-Type Double Patenting Rejection

Claims 21-24 have been rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over various claims of U.S. Patent Nos. 8,541,451; 9,226,896; 9,415,041; and 10,100,013; all in view of Axt, et al. WO 2006/099165 A1; and over various claims in U.S. Patent Nos. 8,754,225; 8,921,396; and 9,765,028. In response, Applicants are submitting herewith terminal disclaimers in compliance with 37 C.F.R. §1.321(c).

Applicants note that the filing of a terminal disclaimer to obviate a rejection based on nonstatutory double patenting is not an admission of the propriety of the rejection. *Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870, 20 U.S.P.Q.2d 1392 (C.A.F.C. 1991). Specifically, the courts have indicated that the "filing of a terminal

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Attorney Docket No. P-257-US7  
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disclaimer simply serves the statutory function of removing the rejection of double patenting, and raises neither a presumption nor estoppel on the merits of the rejection."

Should there be any questions regarding this paper or this application, the Examiner is encouraged to telephone the undersigned attorney for Applicants at (650) 808-6406.

Respectfully submitted,

Date: July 10, 2019

By: /Jeffrey A. Hagenah/  
Jeffrey A. Hagenah, Ph.D.  
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**AMENDMENTS TO THE CLAIMS:**

This listing of the claims will replace all prior versions, and listings, of claims in the application.

1-20. (Canceled)

21. (Previously Presented) A crystalline freebase of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester having a melting point of about 125 °C.

22. (Currently Amended) A crystalline freebase of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester having a differential scanning calorimetry thermogram substantially in accordance with that shown in FIG. 4.

23. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and crystalline freebase of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester having a melting point of about 125 °C.

24. (Currently Amended) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and crystalline freebase of biphenyl-2-ylcarbamic acid 1-(2-{[4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl]methylamino}ethyl)piperidin-4-yl ester having a differential scanning calorimetry thermogram substantially in accordance with that shown in FIG. 4.



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27038 7590 09/17/2019

THERAVANCE BIOPHARMA US, INC.  
 901 GATEWAY BOULEVARD  
 SOUTH SAN FRANCISCO, CA 94080

EXAMINER

PIHONAK, SARAH

ART UNIT

PAPER NUMBER

1627

DATE MAILED: 09/17/2019

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/130,079	09/13/2018	Grahame Woollam	P-257-US7	9930

TITLE OF INVENTION: CRYSTALLINE FREEBASE FORMS OF A BIPHENYL COMPOUND

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1000	\$0.00	\$0.00	\$1000	12/17/2019

**THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.**

**THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.**

### HOW TO REPLY TO THIS NOTICE:

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III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

**IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at [www.uspto.gov/PatentMaintenanceFees](http://www.uspto.gov/PatentMaintenanceFees).**

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(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/130,079	09/13/2018	Grahame Woollam	P-257-US7	9930

#### TITLE OF INVENTION: CRYSTALLINE FREEBASE FORMS OF A BIPHENYL COMPOUND

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1000	\$0.00	\$0.00	\$1000	12/17/2019

EXAMINER	ART UNIT	CLASS-SUBCLASS
PIHONAK, SARAH	1627	514-316000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

"Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

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1 \_\_\_\_\_

2 \_\_\_\_\_

3 \_\_\_\_\_

#### 3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent):  Individual  Corporation or other private group entity  Government

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4b. Method of Payment: (Please first reapply any previously paid fee shown above)

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#### 5. Change in Entity Status (from status indicated above)

- Applicant certifying micro entity status. See 37 CFR 1.29
- Applicant asserting small entity status. See 37 CFR 1.27
- Applicant changing to regular undiscounted fee status.

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NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature \_\_\_\_\_

Date \_\_\_\_\_

Typed or printed name \_\_\_\_\_

Registration No. \_\_\_\_\_



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/130,079	09/13/2018	Grahame Woollam	P-257-US7	9930
27038	7590	09/17/2019	EXAMINER	
<b>THERAVANCE BIOPHARMA US, INC.</b> 901 GATEWAY BOULEVARD SOUTH SAN FRANCISCO, CA 94080				PIHONAK, SARAH
		ART UNIT		PAPER NUMBER
1627				

DATE MAILED: 09/17/2019

**Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)**  
 (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

## **OMB Clearance and PRA Burden Statement for PTOL-85 Part B**

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

### **Privacy Act Statement**

**The Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b) (2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

<b><i>Notice of Allowability</i></b>	Application No. 16/130,079	Applicant(s) Woollam, Grahame	
	Examiner SARAH PIHONAK	Art Unit 1627	AIA (FITF) Status No

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--**

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1.  This communication is responsive to 7/10/19.
- A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on \_\_\_\_\_.
2.  An election was made by the applicant in response to a restriction requirement set forth during the interview on \_\_\_\_\_; the restriction requirement and election have been incorporated into this action.
3.  The allowed claim(s) is/are 21-24. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see [http://www.uspto.gov/patents/init\\_events/pph/index.jsp](http://www.uspto.gov/patents/init_events/pph/index.jsp) or send an inquiry to **PPHfeedback@uspto.gov**.
4.  Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

**Certified copies:**

- a)  All      b)  Some      \*c)  None of the:

1.  Certified copies of the priority documents have been received.
2.  Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3.  Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\* Certified copies not received: \_\_\_\_\_.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

5.  CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
  - including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date \_\_\_\_\_.

**Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).**
6.  DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

**Attachment(s)**

- |   |  |
|---|--|
| 1. <input type="checkbox"/> Notice of References Cited (PTO-892)  | 5. <input type="checkbox"/> Examiner's Amendment/Comment                             |
| 2. <input type="checkbox"/> Information Disclosure Statements (PTO/SB/08),<br>Paper No./Mail Date _____.          | 6. <input checked="" type="checkbox"/> Examiner's Statement of Reasons for Allowance |
| 3. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit<br>of Biological Material _____. | 7. <input type="checkbox"/> Other _____.   |
| 4. <input type="checkbox"/> Interview Summary (PTO-413),<br>Paper No./Mail Date. _____.                           |  |

/SARAH PIHONAK/  
Primary Examiner, Art Unit 1627

***Notice of Pre-AIA or AIA Status***

The present application is being examined under the pre-AIA first to invent provisions.

***Status of Claims***

1. Claims 21-24 are pending as of the reply and amendments filed on 7/10/19. Claims 1-20 have been canceled.

The rejection of claims 22 and 24 under 35 USC 112, second paragraph is withdrawn in view of the amendments to the claims.

The terminal disclaimer filed on 7/10/19 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US patents 8541451, 8754225, 8921396, 9226896, 9415041, 9765028, and 10100013 has been reviewed and is accepted. The terminal disclaimer has been recorded.

The rejections for nonstatutory double patenting over the claims of US patents 8541451, 8754225, 8921396, 9226896, 9415041, 9765028, and 10100013 are withdrawn in view of the acceptance of the terminal disclaimer.

Applicants' arguments and evidence regarding the 103 rejections over Axt, WO 2006099165, and over Mammen, US 20050203133 have been fully considered and are found persuasive; the 103 rejections of record are withdrawn.

2. Claims 21-24 are allowed.

***Reasons for Allowance***

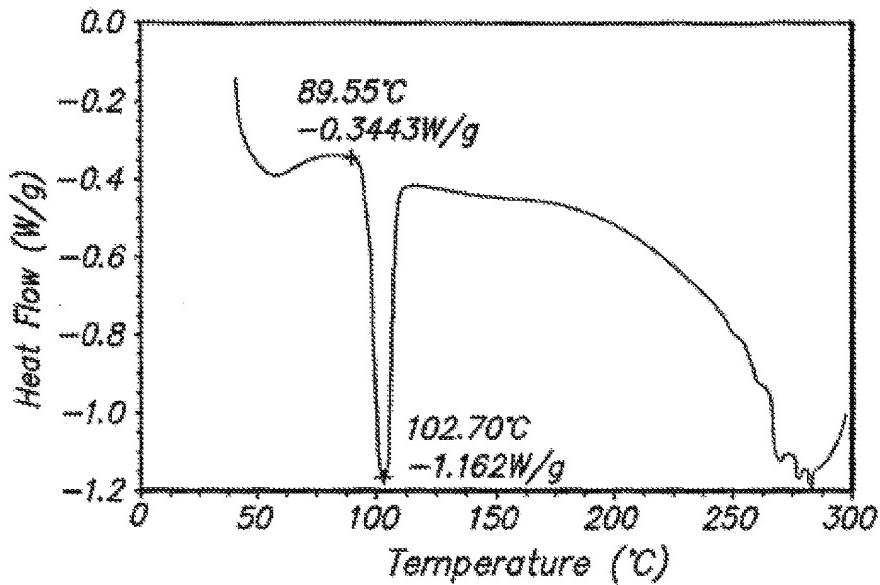
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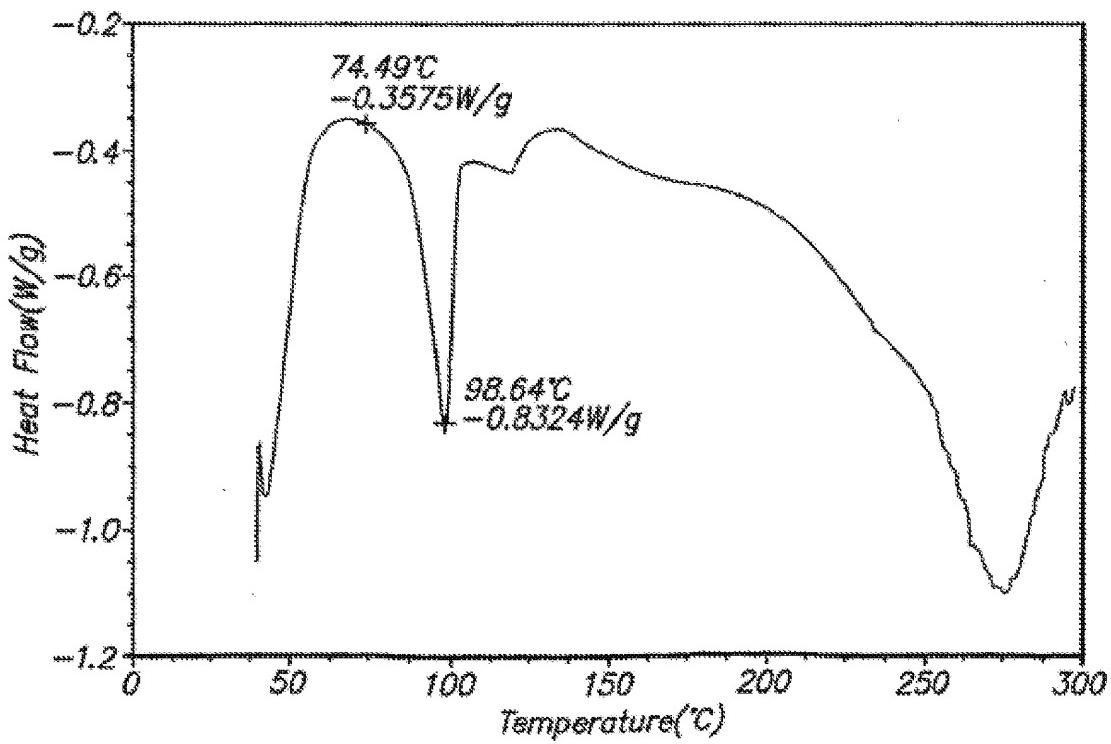
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3. The following is an examiner's statement of reasons for allowance: the claimed crystalline freebase of biphenyl-2-ylcarbamic acid 1-(2-{{4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl)methylamino}ethyl)piperidin-4-yl ester having a melting point of about 125 °C, and the differential scanning calorimetry thermogram in accordance with that shown in Fig. 4, corresponding to polymorph form III is not taught or suggested by the closest prior art, Axt, WO 2006099165, and Mammen, US 20050203133 (both of previous record). Axt teaches crystalline polymorphs I and II of freebase biphenyl-2-ylcarbamic acid 1-(2-{{4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl)methylamino}ethyl)piperidin-4-yl ester; however, these polymorphs are prepared by different processes (different solvents) from the instantly claimed crystalline polymorph, are characterized by different PXRD patterns, and the polymorphs of Axt have melting peaks at about 102.7 °C and 98.6 °C, respectively, as well as DSC trace that are distinct from Fig. 4. Figs. 19 and 24, shown below, represent the DSC trace of forms I and II of Axt, compared to the DSC thermogram of Fig. 4 of the claimed polymorph of the instant claims:

**FIG. 19**



**FIG. 24**



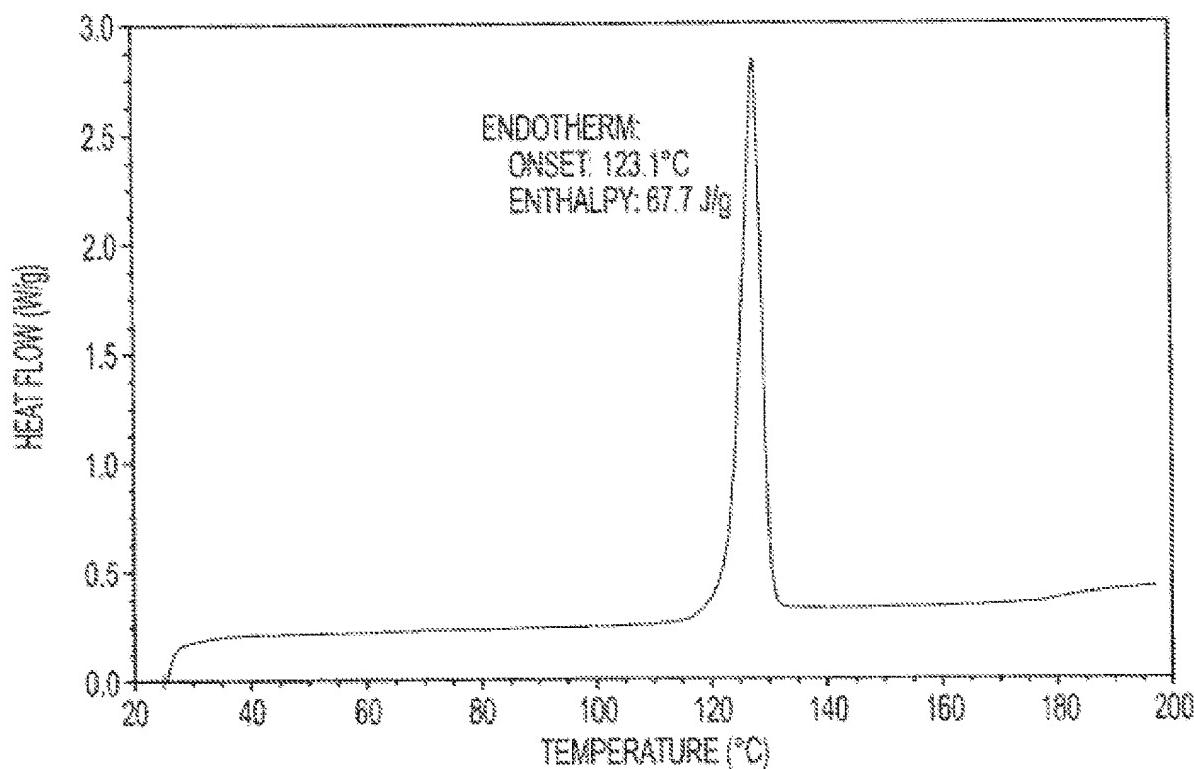


FIG. 4

Mammen teaches crystalline freebase biphenyl-2-ylcarbamic acid 1-(2-{{4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl)methylamino}ethyl)piperidin-4-yl ester, however, this crystalline form is taught to be prepared by a different process compared to the instantly claimed crystalline form, using different solvents (Mammen teaches a combination of H<sub>2</sub>O:acetonitrile at a 1:1 ratio or a combination of acetonitrile: MTBE at a 1:2 ratio, while the instantly claimed form is prepared using only acetonitrile, toluene, or a combination of isopropyl acetate:water). Mammen also does not teach or suggest the crystalline form having a melting point of about 125 °C or the DSC thermogram of Fig. 4. The claimed crystalline form of freebase biphenyl-2-ylcarbamic acid 1-(2-{{4-(4-carbamoylpiperidin-1-ylmethyl)benzoyl)methylamino}ethyl)piperidin-4-yl ester having a melting point of about 125

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°C, and the differential scanning calorimetry thermogram in accordance with that shown in Fig. 4 is therefore not taught or suggested by the prior art.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

***Conclusion***

4. Claims 21-24 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARAH PIHONAK whose telephone number is (571)270-7710. The examiner can normally be reached on Monday-Friday 9:00-5:30 EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

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may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SARAH PIHONAK/  
Primary Examiner, Art Unit 1627